

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P734PC00	FOR FURTHER ACTION		See Form PCT/PEAA16
International application No. PCT/DK2004/000259	International filing date (day/month/year) 07.04.2004	Priority date (day/month/year) 11.04.2003	
International Patent Classification (IPC) or national classification and IPC C07K14/47, A61K39/00, C07K16/30, C12N5/06			
Applicant KRAEFTENS BEKAEMPELSE, et al.			
1. This report is the International preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 9 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 7 sheets, as follows: <input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). <input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).			
4. This report contains Indications relating to the following items: <input checked="" type="checkbox"/> Box No. I Basis of the opinion <input type="checkbox"/> Box No. II Priority <input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input checked="" type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application			
Date of submission of the demand 11.02.2005		Date of completion of this report 21.07.2005	
Name and mailing address of the International preliminary examining authority: <div style="display: flex; align-items: center;"> <div> European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 </div> </div>		Authorized Officer Huber, A Telephone No. +49 89 2399-8173	



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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-78 as originally filed

Sequence listings part of the description, Pages

1-66 as originally filed

Claims, Numbers

1-53 received on 15.02.2005 with letter of 11.02.2005

Drawings, Sheets

1/5-5/5 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 14-18, 41-46 (IA)

because:

☒ the said international application, or the said claims Nos. 14-18, 41-46 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees, the applicant has:
- ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-53
	No: Claims	
Inventive step (IS)	Yes: Claims	1-53
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-13, 19-40, 47-53
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed
 - ☒ filed together with the international application in computer readable form
 - ☐ furnished subsequently to this Authority for the purposes of search and/or examination
 - ☐ received by this Authority as an amendment on
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional observations, if necessary:

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 14-18 and 41-46 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

For the assessment of the above claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV

Lack of unity of invention

Claim 1 relates to 4 different peptides derived from ML-IAP which have to be capable of raising a specific T-cell response. D1 already discloses two decamers derived from ML-IAP which are capable of eliciting a T cell response. The different peptides of Claim 1 are therefore not linked by a common novel and inventive concept.

Although the applicant has not been invited to pay additional examination fees, he is informed that the objection will be prosecuted during regional phase examination at the EPO.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability;

citations and explanations supporting such statement

1. The following documents are referred to in this communication:

D1 : SCHMOLLINGER JAN C ET AL: "Melanoma inhibitor of apoptosis protein (ML-IAP) is a target for immune-mediated tumor destruction." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 100, no. 6, 18 March 2003 (2003-03-18), pages 3398-3403, XP002293965 ISSN: 0027-8424

D2 : ANDERSEN M H ET AL: "Spontaneous cytotoxic T-cell responses against survivin-derived MHC class I-restricted T-cell epitopes in situ as well as ex vivo in cancer patients" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 61, no. 16, 15 August 2001 (2001-08-15), pages 5964-5968, XP002283854 ISSN: 0008-5472

D3 : WO 00/03693 A (JENNER BIOTHERAPIES INC) 27 January 2000 (2000-01-27)

D4: JP2002284797 A (HOKKAIDO TLO KK) 03 October 2002

2. Document D1 shows that ML-IAP is a target for immune-mediated tumour destruction. CD4 and CD8 T cells specific for ML-IAP are disclosed. A tumour patient that was vaccinated with ML-IAP developed antibodies of different isotypes and ML-IAP-specific cytotoxic T cells. Also two peptides (decamers) derived from ML-IAP showed high-affinity binding in T2 cell based assays (see p. 3402, Fig. 3).

D2 discloses survivin epitopes which are recognized by cytotoxic T cells. Survivin-based vaccination is suggested.

Also D3 concerns the use of vaccines comprising survivin epitopes for eliciting an antitumour immune response. Antibody-dependent cell mediated cytotoxicity was shown to effect lysis of tumour cells that present survivin antigens on their surface.

D4 discloses the use of a nonapeptide derived from survivin which is capable of inducing cytotoxic T-cells. The peptide is said to be useful in the treatment of cancer.

3. Novelty (Art. 33(2) PCT):

- 3.1 The specific peptides of Claims 1-13 have not been disclosed in the prior art. The method of independent Claim 14 differs from the method of D1, where the T cell response to ML-IAP and two specific fragments thereof was tested in a patient immunized with tumour cells expressing GM-CSF, while the individual according to Claim 14(a) has not been subjected to immune therapy before testing the specific T cell responses against fragments of ML-IAP. Since all other claims refer to the specific peptides according to Claim 1-13, novelty of Claims 1-53 is acknowledged.

4. Inventive step (Art. 33(3) PCT):

- 4.1 Claim 1 is directed to specific peptides derived from ML-IAP which are capable of raising a specific T-cell response. D1, which is considered to represent the most relevant state of the art for assessing inventive step of Claim 1, also discloses ML-IAP peptides which are capable of eliciting a T cell response. In addition, it was known from D2 that peptides of another inhibitor of apoptosis protein (survivin) are capable of eliciting cytotoxic T-cell responses and that survivin peptides may therefore be attractive for tumour vaccination.

Present application differs from the subject-matter of D1 in that further peptides derived from ML-IAP have been identified which are capable of raising a specific T-cell response.

The problem to be solved by the present invention may therefore be regarded as the identification of further peptides derived from ML-IAP which are capable of eliciting a T cell response.

The problem has been solved by applying the ELISPOT assay for the determination of fragments capable of raising a specific T-cell response. This assay has already been successfully applied in D1 and in D2 for analysing the specific T cell response of ML-IAP and the two peptides derived therefrom or of survivin peptides. It would

not require any inventive activity to apply the analogous approach for the identification of further ML-IAP-derived peptides.

Therefore, an inventive step can only be acknowledged if the claimed peptides are superior to the peptides known from D1.

The peptides of Claim 1 have been selected from numerous other fragments of ML-IAP by virtue of their ability to give very strong spontaneous T-cell responses in tumour infiltrating lymphocytes. The claimed peptides are equivalent if not superior to the two peptides disclosed in D1 which were only detectable in a patient after several immunizations with tumour cells expressing GM-CSF.

The data in Fig. 2 show that the peptide ML-IAP90 (= peptide JS90 of D1) displayed lower reactivity in most of the patients tested than peptides ML-IAP280 (SEQ ID NO: 298), ML-IAP245 (SEQ ID NO: 297) and ML-IAP230 (SEQ ID NO: 301).

In addition, MLIAP₂₄₅₋₂₅₃ (SEQ ID NO: 245) appears to be the first HLA-A3 restricted peptide derived from ML-IAP.

Moreover, it was not predictable from the prior art which of the numerous peptides derived from ML-IAP would actually be useful for eliciting a strong T-cell response.

The selection of further suitable peptides does therefore not seem to be obvious.

It can therefore be accepted that the claimed peptides involve the required inventive step.

The method of Claim 14 differs from the method employed in D1 in that it includes the step of testing the naturally occurring T-cell response in cells from a cancer patient who has not been subject to immune therapy. This step has not been envisaged in D1. Therefore, an inventive step can also be acknowledged for the subject-matter of Claim 14.

Claims

1. A polypeptide fragment capable of raising a specific T-cell response, said fragment comprising a peptide selected from the group consisting of rleertck (SEQ ID NO:245), rleertckv (SEQ ID NO:297), qlcpicrapv (SEQ ID NO:298), vleppgardv (SEQ ID NO:301) and functional equivalents having at least 75% sequence identity thereto; wherein said polypeptide fragment comprises at the most 15 amino acids.
2. The polypeptide fragment according to claim 1, wherein said functional equivalent comprises substitutions only in the preferred positions and only to preferred amino acid residues for a given HLA allele as identified in table 2.
3. The polypeptide fragment according to claim 1, wherein said polypeptide fragment comprises at the most 10 amino acids.
4. The polypeptide fragment according to any of claims 1 to 3, wherein the specific T-cell response is measured as more than 50 peptide specific spots per 10^6 cells in an ELISPOT assay performed without pre-stimulation in vitro.
5. The polypeptide fragment according to any of claims 1 to 3, wherein the specific T-cell response is measured as more than 50 peptide specific spots per 10^5 cells in an ELISPOT assay performed after stimulation in vitro.
6. The polypeptide fragment according to any of claims 1 to 3, wherein the specific T-cell response is measured as more than 50 peptide specific spots per 10^6 cells in an ELISPOT assay performed using PBL from an individual that has not been subjected to immune therapy against a neoplastic disease.
7. The polypeptide fragment according to any of claims 1 to 3, wherein the polypeptide fragment is characterised by having a C_{50} value, measured as the concentration (μ M) of the polypeptide fragment required for half maximal binding to a MHC (Major Histocompatibility Complex) class I molecule.

8. The polypeptide fragment according to claim 7, wherein the polypeptide fragment is characterised by having a C_{50} value, measured as the concentration (μM) of the polypeptide fragment required for half maximal binding to an MHC class I molecule, of less than 1000.

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9. The polypeptide fragment according to any of claims 7 and 8, wherein the polypeptide fragment is characterised by having a C_{50} value, measured as the concentration (μM) of the polypeptide fragment required for half maximal binding to an MHC class I molecule, of less than 100.

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10. A polypeptide fragment according to any of claims 7 to 9, wherein the polypeptide fragment is characterised by having a C_{50} value, measured as the concentration (μM) of the polypeptide fragment required for half maximal binding to an MHC class I molecule, of less than 31.

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11. A polypeptide fragment according to any of claims 7 to 10, wherein the polypeptide fragment is characterised by having a C_{50} value, measured as the concentration (μM) of the polypeptide fragment required for half maximal binding to an MHC class I molecule, of less than 5.

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12. A polypeptide fragment according to any of claims 1 to 11, wherein the fragment is capable of activating T-cell growth in vitro.

13. A polypeptide fragment according to claim 12, wherein the fragment is capable of activating T-cell growth in vitro so that more than 10^5 antigen specific CTLs may be harvested after 4 stimulation cycles starting with 10^4 PBMC

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14. A method of selecting a peptide comprising a fragment of ML-IAP for use in a vaccine composition comprising the steps of

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- i) Providing an individual who has not been subjected to immune therapy
- ii) Providing a polypeptide fragment comprising a peptide consisting of at least 9 consecutive amino acid residues of ML-IAP (SEQ ID NO:1),

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- iii) Testing specific T-cell responses against fragments of ML-IAP in said individual
- iv) Selecting fragments of ML-IAP wherein said T-cell response corresponds to or is better than a predetermined selection criterium.

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15. The method according to claim 14, wherein said peptide is selected from the group consisting of rlqeertck (SEQ ID NO:245), qilgqlrpl (SEQ ID NO:55), ltaevppel (SEQ ID NO:100), gmgseelrl (SEQ ID NO:84), elptprev (SEQ ID NO:200), rlqeertckv (SEQ ID NO:297), qlcpicrapv (SEQ ID NO:298), llrskgrdfv (SEQ ID NO:300), vleppgardv (SEQ ID NO:301) and pltaevppel (SEQ ID NO:302).

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16. The method according to claim 15, wherein said polypeptide fragment comprises at the most 15 amino acids.

17. The method according to claim 14, wherein testing said T-cell response comprises an ELISPOT assay.

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18. The method according to claim 17, wherein said predetermined selection criterium is more than 50 peptide specific spots per 10^6 cells in said ELISPOT assay.

19. A polypeptide fragment according to any of claims 1 to 13 for use as a medicament.

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20. Use of one or more polypeptide fragments according to any of claims 1 to 13 in the manufacture of a medicament for treatment of a clinical condition in an individual in need thereof.

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21. Use according to claim 20, wherein said clinical condition is cancer.

22. Use according to claim 21, wherein the cancer is malignant melanoma.

23. Use according to claim 20, wherein said clinical condition is an auto-immune disease.

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24. Use according to any of claims 20 to 23, wherein at least one of said polypeptide fragments is restricted to an HLA molecule present in said individual.
- 5 25. Use according to any of claims 20 to 24, wherein said individual has not previously been subjected to immune therapy against a neoplastic disease.
26. A medicament for treating a clinical condition comprising a polypeptide according to any of claims 1 to 13 as an active ingredient.
- 10 27. A vaccine composition comprising an isolated polypeptide comprising a peptide selected from the group consisting of rleertck (SEQ ID NO:245), rleertckv (SEQ ID NO:297), qlcpicrapv (SEQ ID NO:298), vleppgardv (SEQ ID NO:301) and functional equivalents having at least 75% sequence identity thereto; and a pharmaceutically acceptable carrier and/or adjuvant.
- 15 28. The vaccine composition according to claim 27, wherein said composition comprises at least one polypeptide fragment according to any of claims 1 to 13.
- 20 29. The vaccine composition according to any of claims 27 to 28 further comprising an adjuvant.
30. The vaccine composition according to claim 29, wherein the adjuvant is selected from the group consisting of Montanide ISA-51 and QS-21
- 25 31. The vaccine composition according to any of claims 27 and 28, wherein the composition further comprises a carrier.
32. The vaccine composition according to claim 31, wherein the carrier is a dendritic cell.
- 30 33. The vaccine compositions according to claim 27 to 28, wherein the composition comprises more than one different ML-IAP fragment according to any of claims 1 to 13.

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34. The vaccine composition according to claim 33, wherein the composition comprises different ML-IAP fragments, wherein said fragments are capable of associating with the most frequently occurring MHC class I molecules.
- 10
35. The vaccine composition according to claim 33, wherein the composition comprises at least 2 different ML-IAP fragments each capable of associating with a different HLA molecule selected from the group consisting of HLA-A2, HLA-A1, HLA-A3, HLA-A24, HLA-B7, HLA-B27 and HLA-B44.
- 15
36. The vaccine composition according to claim 35, wherein the composition comprises at least one class I-restricted ML-IAP peptide and at least one class II-restricted ML-IAP peptide.
- 20
37. A pharmaceutical composition comprising the vaccine composition according to any of claims 27 to 36 and an anti-cancer medicament.
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38. The pharmaceutical composition according to claim 37, wherein the anti-cancer medicament is selected from the group consisting of chemotherapeutic agents and immunotherapeutic agents.
- 30
39. A kit-of parts comprising comprising a polypeptide comprising a peptide selected from the group consisting of rleertck (SEQ ID NO:245), rleertckv (SEQ ID NO:297), qlcpicrapv (SEQ ID NO:298), vleppgardv (SEQ ID NO:301) and functional equivalents having at least 75% sequence identity thereto; and a bioactive compound selected from the group consisting of a chemotherapeutic agent, an immunotherapeutic agent, and a second cancer vaccine composition.
40. The kit-of-parts according to claim 39 comprising one or more polypeptide fragments according to any of claims 1 to 13.
41. A method for treatment of an individual diagnosed with cancer, said method comprising the step of administering to the individual the polypeptide fragment according to any of claims 1 to 13, or the vaccine composition according to any of

claims 27 to 36, or the pharmaceutical composition according to any of claims 37 and 38 or the kit of parts according to any of claims 39 and 40.

5 42. The method according to claim 41, wherein said individual has not previously been subjected to immune therapy against a neoplastic disease.

43. The method according to claim 41, wherein said cancer is malignant melanoma.

10 44. A method for prophylactic treatment of an individual at risk of developing a cancer, said method comprising the step of administering to the individual the polypeptide fragment according to any of claims 1 to 13, or the vaccine composition according to any of claims 27 to 36, or the pharmaceutical composition according to any of claims 37 and 38 or the kit of parts according to any of claims 39 and 40.

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45. A method for raising a specific T-cell response against an epitope of ML-IAP (SEQ ID NO:1) in an individual, said method comprising the steps of administering to the individual a polypeptide fragment according to any of claims 1 to 13, and raising a specific T-cell response against an epitope of ML-IAP in
20 the individual.

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25 46. The method according to claim 45, wherein the methods comprises administering one or more polypeptide fragments according to any of claims 1 to 13, and wherein at least one fragment is restricted to an HLA molecule present in said individual.

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47. An antibody capable of specific recognition of a polypeptide fragment according to any of claims 1 to 13.

30 48. A method for activating and expanding T-cells specific for ML-IAP or fragments thereof comprising the steps of co-cultivating T-cells and one or more polypeptide fragments according to any of claims 1 to 13.

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49. The method according to claims 48, wherein the method comprises generating and loading monocyte-derived dendritic cells (DC) with said polypeptide fragment(s) and co-cultivating said DC and periferal blood monocytes (PBMC) comprising T-cells.
- 5
50. The method according to claim 48, wherein the method comprises generating *Drosophila melanogaster* cells expressing one or more different HLA molecules, loading said *Drosophila melanogaster* cells with said polypeptide fragment(s) and co-cultivating said *Drosophila* cells with periferal blood monocytes (PBMC) comprising T-cells or T-cells purified from PBMC.
- 10
51. ML-IAP specific T-cells obtained by the method according to any of claims 48 to 50.
- 15
52. T-cells according to claim 51, wherein said ML-IAP specific T-cells are cytotoxic T-cells.
53. Use of ML-IAP specific T-cells according to any of claims 52 and 53 for the preparation of a medicament for treatment of a clinical condition in an individual in need thereof.
- 20